Original article

Induction Chemotherapy and Chemoradiotherapy Combined to ASA vs. Placebo for High-Risk Rectal Cancer: Results of a Randomized Trial

Juliana Ominelli,[1] Rodrigo O. de Castro Araujo,[2] Marcus Valadão,[2] Monica L.A. Padoan,[1] Victor M. Lopes dos Santos,[1] Jamille G. Dutra,[1] Claudia C. Torres,[3] Monique A. Barbosa,[3] Raquel Guimarães,[4] Juliana C. Carneiro Carvalho,[4] Maria A. Ferreira,[5] Ivanir M. de Oliveira,[6] Isabele Small,[1] Andréia C. de Melo,[1] Luiz H. Araujo[1]

Abstract

The ICAR trial aimed to evaluate induction chemotherapy followed by chemoradiotherapy with or without ASA on MRI tumor response. This single-center, double-blind, randomized phase II trial evaluated induction treatment with CAPOX, followed by capecitabine-based chemoradiotherapy with ASA (arm 1) or placebo (arm 2) in 27 patients. ASA during chemoradiotherapy was safe but failed to improve MRI tumor response.

Induction: chemotherapy (IC) followed by chemoradiation (CRT) is an attractive approach in high-risk locally advanced rectal cancer. Additionally, ASA has shown potential to improve outcomes alongside CRT in rectal cancer. The ICAR trial aimed to evaluate the safety and efficacy of IC followed by CRT with or without ASA on MRI tumor response. **Methods:** Single-center, double-blind, randomized phase II trial to evaluate induction treatment with CAPOX, followed by capecitabine-based chemoradiotherapy with ASA (arm 1) or placebo (arm 2) in high-risk stage II-III rectal adenocarcinoma staged by MRI. The primary endpoint was MRI tumor regression grade (mrTRG). Secondary endpoints were pathological response, surgical outcomes, postoperative complications, treatment tolerance, DFS, and OS. **Results:** Between January 2018 and August 2019, 27 patients were eligible, 25 (92.5%) completed IC, and 23 patients were randomly assigned (12 to ASA group; 11 to placebo group). In the ASA arm, 3 pts (25%) presented distant disease progression at restaging. Seven patients (30.4%) had cCR after neoadjuvant treatment. All 13 patients submitted to surgery after neoadjuvant treatment underwent R0 resections except for 1 patient with positive CRM, and 12 patients (92.3%) had sphincter preservation. After a median follow-up of 34.9 months, the 2-year DFS was 83.1% and 3-year OS was 81.5%. **Conclusion:** There was good compliance in both treatment arms and encouraging cCR rate. ASA during CRT was safe but failed to improve on MRI tumor response. The study was closed due to the absence of benefits.

Clinical Colorectal Cancer, Vol. 000, No.xxx, 1–9
Keywords: Acetylsalicylic acid, Locally advanced rectal cancer, Total neoadjuvant therapy, Neoadjuvant acetylsalicylic acid, Neoadjuvant chemotherapy

Introduction

The standard of care for locally advanced rectal cancer (LARC) consists of neoadjuvant fluoropyrimidine-based chemoradiotherapy (CRT) followed by total mesorectal excision (TME) and adjuvant chemotherapy. The neoadjuvant approach provides low local recur-

[1]Division of Clinical Research, Instituto Nacional de Câncer (INCA), Rio de Janeiro (RJ), Brazil
[2]Department of Abdomino-Pelvic Surgery, Instituto Nacional de Câncer (INCA), Rio de Janeiro (RJ), Brazil
[3]Department of Radiology, Instituto Nacional de Câncer (INCA), Rio de Janeiro (RJ), Brazil
[4]Department of Radiotherapy, Instituto Nacional de Câncer (INCA), Rio de Janeiro (RJ), Brazil
[5]Department of Endoscopy, Instituto Nacional de Câncer (INCA), Rio de Janeiro (RJ), Brazil
[6]Department of Pathology, Instituto Nacional de Câncer (INCA), Rio de Janeiro (RJ), Brazil

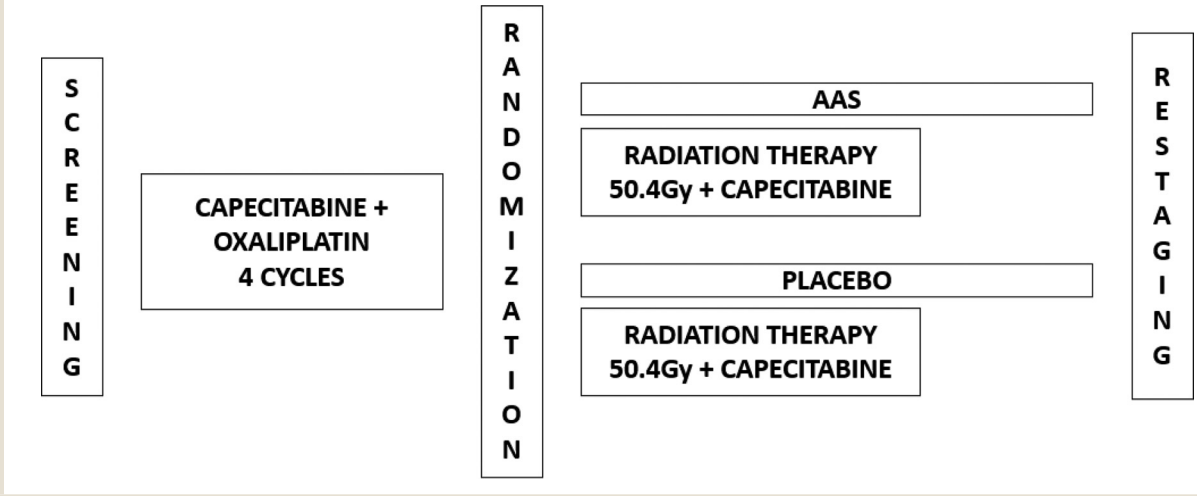
Submitted: Mar 4, 2022; Revised: Apr 26, 2022; Accepted: May 6, 2022; Epub: xxx

Address for correspondence: Juliana Ominelli, MD, Rua André Cavalcanti, 37, sexto andar prédio anexo, Centro, Rio de Janeiro – RJ, Brazil, 20.230-050. Phone: +55 21 3207-6564. Fax: +55 21 3207-6650
E-mail contact: juominelli@hotmail.com

1533-0028/$ - see front matter
https://doi.org/10.1016/j.clcc.2022.05.002

Please cite this article as: Juliana Ominelli et al, Induction Chemotherapy and Chemoradiotherapy Combined to ASA vs. Placebo for High-Risk Rectal Cancer: Results of a Randomized Trial, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2022.05.002

Figure 1 Clinical trial design.



rence rates, and reduced toxicity and postoperative complications compared to postoperative treatment.[1,2] However, the LARC estimated 5-year distant recurrence rate of 36% is still worrisome.[1]

The role of adjuvant chemotherapy for LARC after preoperative CRT and TME is still debatable, mainly due to low adherence to postoperative treatment. In prospective trials, only one-third of patients received full planned chemotherapy doses.[3,4] Nevertheless, ADORE trial demonstrated an increase in disease-free survival (DFS) with FOLFOX in patients with poor response to neoadjuvant treatment.[5,6]

Induction chemotherapy (IC) is the strategy of delivering chemotherapy (CT) before neoadjuvant CRT, instead of offering in the adjuvant setting. This approach has been evaluated mainly in patients with locally advanced tumors. The rationale includes treating micrometastasis early, decreasing toxicity rates, and improving downstaging. Previous studies evaluating this strategy found high overall response rate (ORR) and R0 resections.[7] Moreover, compliance to IC was better than to adjuvant chemotherapy without compromising tolerance to CRT.[8]

Acetylsalicylic acid (ASA) is a popular prostaglandin inhibitor often used for cardiovascular disease prevention. Some large cohorts also found a reduction in the incidence of colorectal adenomas and adenocarcinomas in patients taking ASA.[9,10] It is also associated with a lower incidence of metastasis and enhances tumor activity to chemotherapy in chemo resistant colorectal cancer patients.[11,12] ASA inhibits COX enzymes (COX1 and COX2), the blockade of COX1 interferes with platelet action, and COX2 acts in PGE2 formation (a pro-inflammatory enzyme related to tumor growth).[13,14] Platelets seem to promote the protection of tumor cells from the action of natural killer cells and the development of metastases through adhesion and extravasation of tumor cells in the vascular endothelium.[15,16]

In 2015, Restivo et al. published the results of an observational study evaluating the role of chronic ASA in patients submitted to neoadjuvant CRT. Patients with stage II and III rectal cancer assigned to the ASA group had increased downstaging, higher pathological response, better progression-free survival (PFS), and overall survival (OS) compared to the control group.[17] These results suggest that ASA could be explored in stage II-III rectal cancer treatment. The ICAR trial evaluated the impact of IC followed by CRT with or without ASA on tumor response. To our knowledge, this was the first prospective randomized trial to assess the addition of ASA to CRT.

Methods

Study Design and Participants

The ICAR trial was a single-center, double-blind, randomized phase II trial evaluating the safety and efficacy of IC with CAPOX, followed by capecitabine-based CRT with ASA (arm 1) or placebo (arm 2). Fig. 1 illustrates the study design. The Brazilian National Cancer Institute (INCA) conducted this trial after institutional ethics committee approval. All consecutive rectal cancer patients who met eligibility criteria were enrolled. The study followed the Good Clinical Practice Guidelines and each patient provided written informed consent before enrolment. IMEC (Pernambuco, Brazil) pharmaceutics provided ASA/placebo pills. There was no other external funding. ClinicalTrials.gov Identifier: NCT03170115.

Patients

Inclusion Criteria. Eligibility criteria were histologically documented extraperitoneal rectal adenocarcinoma stage II-III, and at least one of the following high-risk factors evaluated by magnetic resonance imaging (MRI): 1. tumor within 1 mm of circumferential resection margin (CRM); 2. mesorectal fat invasion $\geq$ 5mm (T3c-d); 3. adjacent organ invasion (T4); 4. suspicious nodal disease (N$\geq$ 1); 5. extramural venous invasion (EMVI); 6. tumor $\leq$ 5cm from anal verge (AV). Patients were $\geq$ 18 and $\leq$ 75 years of age, had an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1, and had adequate bone marrow, renal and hepatic functions.

Please cite this article as: Juliana Ominelli et al, Induction Chemotherapy and Chemoradiotherapy Combined to ASA vs. Placebo for High-Risk Rectal Cancer: Results of a Randomized Trial, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2022.05.002

Table 1 Patients' Baseline Characteristics

	All Patients n = 27 (%)	ASA Arm (n = 12)	Placebo Arm (n11)
Sex			
Male	19 (70%)	10 (83%)	6 (54%)
Female	8 (30%)	2 (17%)	5 (45%)
Age (yrs)			
Median (range)	55 (33 - 73)	53 (33 - 61)	58 (43-73)
cTNM			
IIA	3 (11%)	0	2 (18%)
IIB	0	0	0
IIC	1 (4%)	0	1 (9%)
IIIA	1 (4%)	0	1 (9%)
IIIIB	11 (41%)	5 (42%)	3 (27%)
IIIIC	11 (41%)	7 (58%)	4 (36%)
MRI-defined high-risk features			
CRM involvement	18 (66%)	9 (75%)	9 (82%)
T3c-T3d	9 (33%)	4 (33%)	3 (27%)
T4	10 (37%)	6 (50%)	4 (36%)
Nodal involvement	20 (74%)	12 (100%)	8 (73%)
EMVI	11 (41%)	6 (50%)	5 (45%)
Lower third tumor	18 (66%)	8 (66%)	10 (91%)
Number of MRI-high risk criteria per patient			
1	0	0	0
2	7 (25.9%)	2 (16.7%)	3 (27.3%)
3	5 (18.5%)	3 (25%)	2 (18.2%)
4	9 (33.3%)	4 (33.3%)	3 (27.3%)
5	6 (22.2%)	3 (25%)	3 (27.3%)

Percentages might be not equal 100% due the rounding.

Patients were excluded if they had received prior treatment for rectal cancer, had a diagnosis of other invasive malignancy in the past 5 years except for non-melanoma skin cancer, any serious or uncontrolled illness, myocardial infarction or cerebrovascular disease in the previous 6 months, neurological and psychiatric disorders, ASA allergy, antiplatelet medication usage in the past 30 days, or increased risk for gastrointestinal bleeding including esophageal varices and peptic ulcer disease.

Procedures

All patients were required to have a chest and abdomen computed tomography (CT) scan, pelvic MRI, and were assessed by a multidisciplinary team before starting IC. Pelvic MRI was repeated after IC and after the completion of neoadjuvant treatment. Two experienced radiologists evaluated all MRI. Patients were randomly assigned in a 1:1 ratio to receive ASA or placebo, stratified by MRI tumor regression grade (mrTRG) after IC. Patients and study team were blinded, including radiologists and pathologists.

Induction Chemotherapy. IC consisted of 4 cycles of intravenous oxaliplatin 130mg/m² on day 1 and oral capecitabine 850mg/m² twice daily for 14-days every 3-weeks. Dose adjustments were made according to observed toxicity based on the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.0. Patients with limiting toxicity to chemotherapy were discontinued.

Table 2 Treatment-Related Grade 3 to 5 Toxicities

Adverse Events	
During Induction Chemotherapy (n:27)	
	Grade ≥ 3
Abdominal sepsis	1 (3.7%)
Pelvic pain	1 (3.7%)
Diarrhea	1 (3.7%)
Vomiting	1 (3.7%)
Neutropenia	1 (3.7%)
Hyperglycemia	1 (3.7%)
Hypertension	3 (11.1%)
During Chemoradiotherapy (n:23)	
	Grade ≥ 3
Radiation dermatitis	3 (13%)
Constipation	1 (4.3%)
Hyperglycemia	1 (4.3%)

Chemoradiotherapy

Three-dimension conformational radiotherapy was delivered in a dose of 50.4Gy, 28 fractions. Oral ASA 100mg or

Please cite this article as: Juliana Ominelli et al, Induction Chemotherapy and Chemoradiotherapy Combined to ASA vs. Placebo for High-Risk Rectal Cancer: Results of a Randomized Trial, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2022.05.002

Table 3 Tumor Regression Grade (TRG)

TRG	ASA Arm			PLACEBO Arm		
	mrTRG		ypTRG N: 8	mrTRG		ypTRG N: 5
	After IC n:12	After CRT n:12*		After IC N:11	After CRT N:11	
TRG 1	0	2 (16.6%)	1 (12.5%)	1 (9%)	4 (36.3%)	0
TRG 2	0	0	1 (12.5%)	0	1 (9%)	1 (20%)
TRG 3	1 (8.3%)	5 (41.6%)	1 (12.5%)	1 (9%)	3 (27.2%)	1 (20%)
TRG 4	5 (41.6%)	3 (25%)	4 (50%)	7 (63.6%)	2 (18.1%)	2 (40%)
TRG 5	6 (50%)	1 (8.3%)	1 (12.5%)	2 (18.1%)	0	1 (20%)
Unknown	0	1 (8.3%)	0	0	1 (9%)	0

*3 patients had distant disease progression despite achieving local response.
Abbreviations: TRG = tumor regression grade; mrTRG = magnetic resonance imaging tumor regression grade; IC = induction chemotherapy; CRT = chemoradiotherapy; ypTRG = pathologic tumor regression grade after neoadjuvant treatment

Table 4 Patients with Disease Progression or Recurrence

Treatment Arm	Recurrence / Progression	Sites of Recurrence/Progression	Time to Progression (Months)	Status	Time to Death (Months)
1	recurrence	Lung and liver	24.1	Alive with disease	-
1	progression	Lung and liver	8.0	Dead	20
1	progression	Lung	7.9	Alive with disease	-
2	recurrence	Local regrowth	13.5	Alive without disease	-
1	progression	Lung	8.9	Alive with disease	-
2	recurrence	local	18.2	Alive with disease	-

placebo was started after randomization and continued daily until surgery. During the radiotherapy phase, patients received oral capecitabine 825mg/m² twice daily.[18] Patients with limiting toxicity to chemotherapy or ASA/placebo could continue with isolated radiotherapy treatment at investigator's discretion

Surgery

Patients were reassessed 8 to 10weeks after CRT with physical examination, pelvic MRI, and rectosigmoidoscopy. Total mesorectal excision (TME) was performed 10 to 12 weeks after radiation therapy. Resection was planned accordingly to the remaining tumor location to secure at least 1mm free CRM and 10mm distal margin. Sphincter was preserved when possible, and minimally invasive access (laparoscopic or robotic) was favored.

Nonoperative Management

A nonoperative approach ("watch and wait") was offered to patients with complete clinical response (cCR) and who were not candidates to sphincter sparing surgery after neoadjuvant treatment. cCR was defined as a good radiological response (mrTRG 1-2) [19] and no clinical residual tumor on endoscopy (ie, absence of ulceration, mass, or mucosal irregularity). Non-operated patients had an intensive follow-up with physical examination and rectosigmoidoscopy every 2 months [20] and pelvic MRI every 4 months. Patients with tumor regrowth were evaluated for salvage surgical resection.

Study's Primary and Secondary Endpoints

The primary endpoint was MRI tumor regression grade (mrTRG) after total neoadjuvant treatment.[21] Good response was defined as mrTRG 1 and 2 and poor response as mrTRG 3 to 5.

Secondary endpoints included clinical response after IC, pathological response in surgically resected specimens using Mandard's classification,[22] surgical outcomes (CRM and mesorectal excision grade), postoperative complications, treatment tolerance, DFS and OS.

Statistical Analysis

The sample size was calculated according to Simon's optimal two-stage design to detect a difference of 26% or greater in good MRI response ($\alpha = 0.05$, 80% power). Eleven patients should be included in each group during the first stage. If 5 patients or less achieved MRI good response (mrTRG 1 or 2), the study should be discontinued.

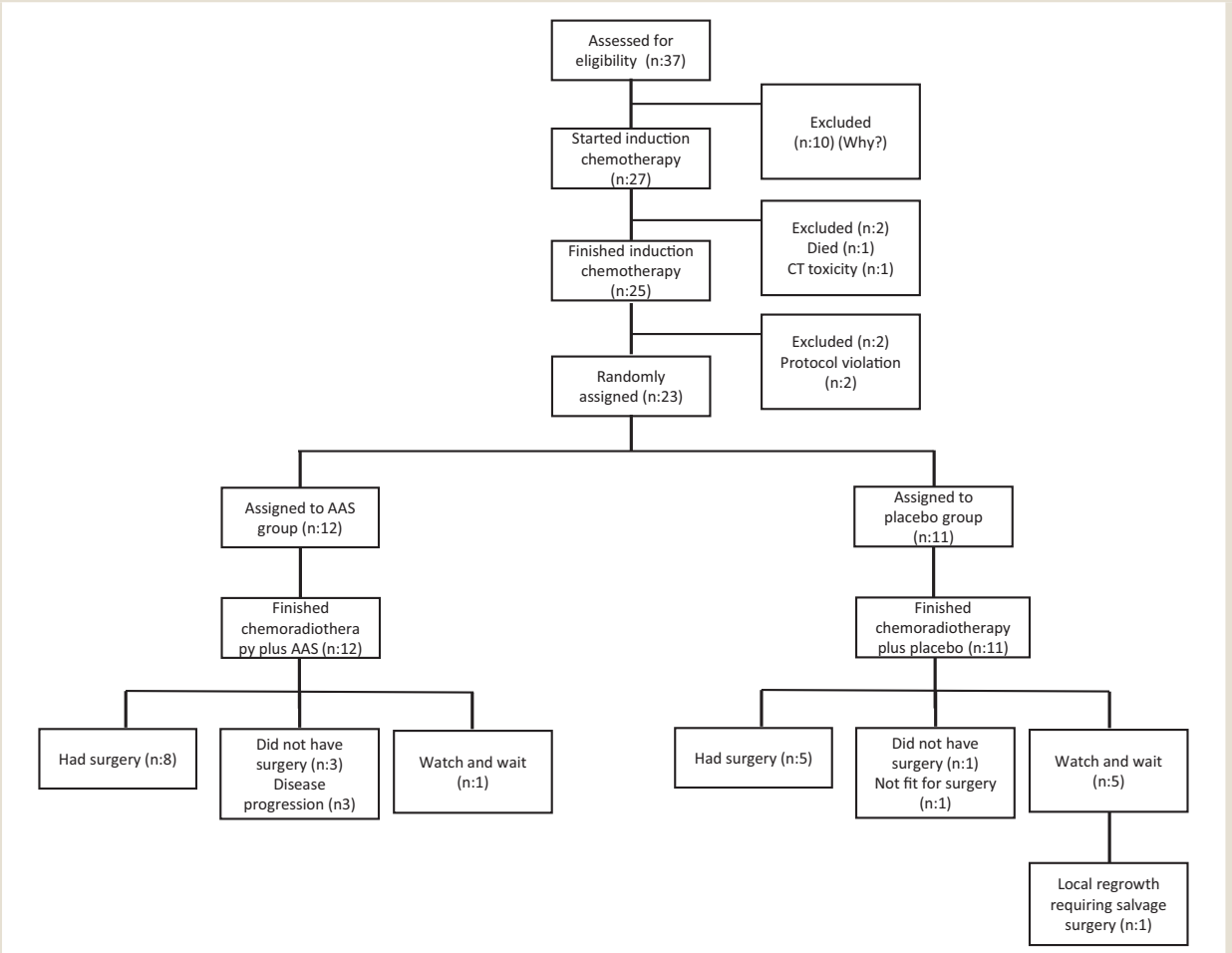
PFS, DFS, and OS were estimated using the Kaplan-Meier method following the Datecan initiative consensus.[23] DFS was considered from the date of surgery or histopathological diagnosis of cCR to an event (anastomotic relapse, metastatic relapse, second primary colorectal cancers and all causes of death), or censorship. OS was calculated from the date of inclusion to any cause of death, or censorship. Endpoints were assessed in the intention-to-treat population. All statistical analysis was performed using SPSS 23.0.

Results

Between January 2018 and August 2019, 37 patients were enrolled, of whom 27 patients (72.9%) were eligible. Ten patients were ineligible due to metastatic disease or for not meeting one of the MRI-risk factors. Fig. 2 shows the participants flow in the trial according to the CONSORT guidelines.

Please cite this article as: Juliana Ominelli et al, Induction Chemotherapy and Chemoradiotherapy Combined to ASA vs. Placebo for High-Risk Rectal Cancer: Results of a Randomized Trial, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2022.05.002

Figure 2 CONSORT flow diagram.



Baseline characteristics are shown in Table 1. Of the 27 eligible patients, 25 (92.5%) finished IC. Two patients had protocol violations before starting the CRT phase and were further excluded. Twenty-three remaining patients were randomized to receive ASA or placebo during CRT. All randomized patients completed the planned radiation therapy and ASA/placebo treatment. Two patients (16.6%) in the ASA arm and 5 (45.4%) in the placebo arm had cCR. Three patients (25%) in the ASA arm did not undergo surgery because of distant disease progression and 1 patient (9%) in the placebo arm was not fit for surgery. At the interim analysis, only 2 patients in the ASA arm and 5 patients in the placebo arm achieved a good radiological response and the study was terminated due to the absence of anticipated treatment response.

Considering symptoms related to the primary tumor, 62% of participants had improvement in diarrhea/constipation, 65% have reduced rectal bleeding and 72% have diminished pelvic pain after the first IC cycle.

Toxicity and Adverse Events

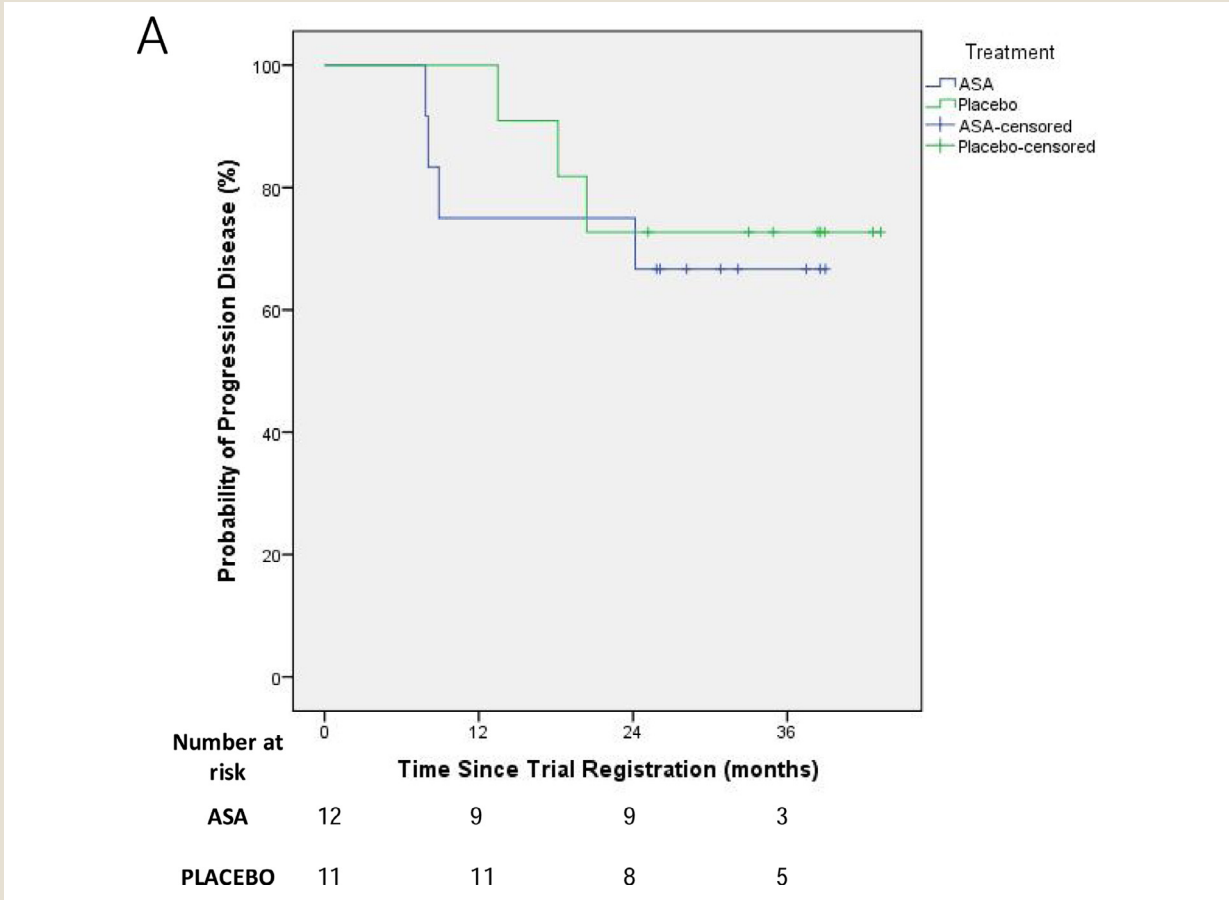
During IC, there was 1 chemotherapy-related death due to abdominal sepsis, and another patient did not finish the entire course of IC due to toxicity. Eight patients had grade 3 adverse events. During CRT, the most frequent grade 3 toxicity was radiation dermatitis. Table 2 lists the incidence of grade 3 to 5 adverse events during neoadjuvant treatment. There was no difference in toxicity between arms.

Clinical and Pathological Response

The median time interval from the end of CRT and restaging MRI was 8.4-weeks (8-40 weeks).) Good radiological response was achieved in 1 patient (4%) after IC and in other 6 patients (24%) after total neoadjuvant treatment. In the ASA arm, 3 patients (25%) presented distant disease progression on restaging despite having a local response (2 patients with mrTRG 3 and 1 patient with mrTRG4). Table 3 lists the radiologic tumor responses in all patients. The median time from the end of CRT and surgery was 14.3-weeks (11-42 weeks). All 13 patients submitted to surgery after neoadjuvant treatment underwent R0 resections except for 1 patient with positive CRM, and 12 patients (92.3%) had sphincter preservation. Eight patients had mesorectal resection grade 3, 4 patients had grade 2, and 1 patient had grade 1. Microscopic residual tumor was found in 2 patients (1 in each arm). Seven patients (30.4%)

Please cite this article as: Juliana Ominelli et al, Induction Chemotherapy and Chemoradiotherapy Combined to ASA vs. Placebo for High-Risk Rectal Cancer: Results of a Randomized Trial, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2022.05.002

Figure 3 Kaplan–Meier Estimates of (A) Progression disease by treatment group, (B) Disease failure by treatment group, (C) Disease failure by treatment group, and (D) Overall survival by treatment group



had cCR after neoadjuvant treatment, from which 6 patients were selected for watch and wait approach, and the operated patient had a complete pathological response (pCR). After nonoperative management, 1 patient had local regrowth and was submitted to salvage resection (abdominal perineal resection - APR) with negative margins. One patient developed local recurrence after sphincter preservation surgery, and also required APR, and negative margins were also achieved in this participant. Therefore, 3 patients (21.4%) underwent curative APR surgery.

After a median follow-up of 34.9-months, among 23 patients randomly assigned to ASA or placebo, 1 patient had local relapse, 4 patients had distant metastases, and 1 last patient had both (local and distant relapse). Sites of disease progression were lung (5 patients), liver (2 patients), and pelvis (1 patient). Table 4 lists patients with disease progression or recurrence. Among patients who completed the assigned treatment protocol, the 2-year DFS was 83.1%. Two-year DFS was 85.7% in the ASA arm and 80.0% in the placebo arm (p:0.5). Two-year PFS was 66.7% in the ASA arm and 72.7% in the placebo arm (p:0.6). Three-year OS was 81.5%. Fig. 3 shows the Kaplan–Meier curves for PFS, DFS, and OS. Five patients (18.5%) died, 4 patients due to rectal cancer and 1 patient due to abdominal sepsis.

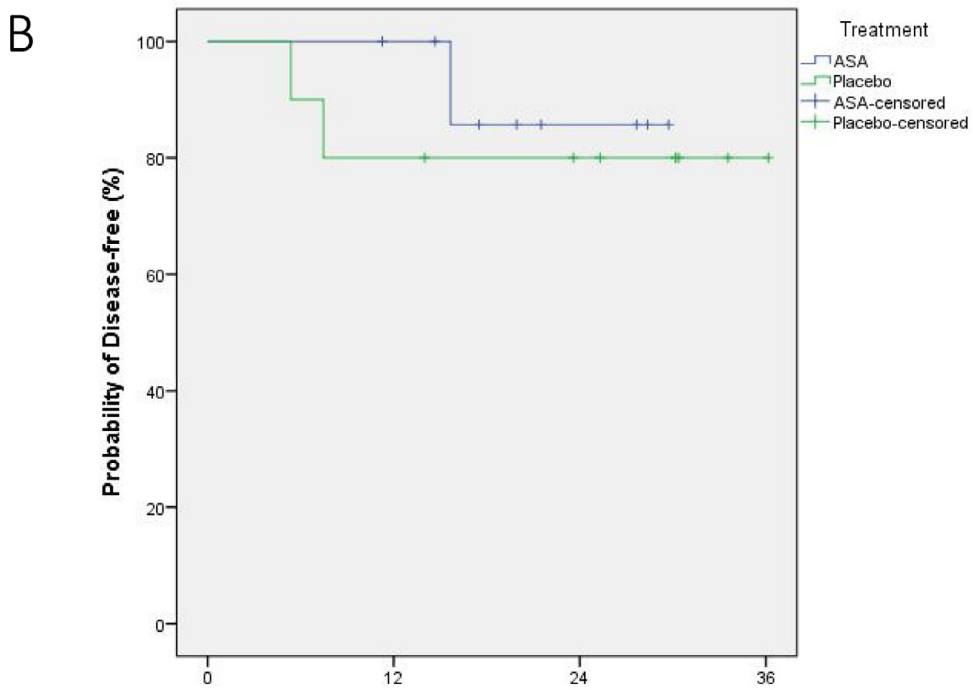
Discussion

In the ICAR trial, there was good compliance to the proposed neoadjuvant treatment that included IC, CRT and either ASA or placebo. More than half of the patients had symptom improvement during the first cycle of IC. Of randomized patients, 30.4% had a cCR. Of patients selected for watch and wait, 71.4% are still in nonoperative management. R0 resection was possible in all patients submitted to surgery and 78.5% underwent sphincter-sparing surgery. Three patients (13%) had disease progression during neoadjuvant treatment in the ASA arm and 3 patients had disease relapse after definitive treatment.

IC allows better adherence than adjuvant chemotherapy. The randomized GCR study compared IC followed by CRT and CRT plus adjuvant chemotherapy. It was shown that 91% of patients completed IC, while 54% completed adjuvant chemotherapy.[8] Previous trials evaluated IC regimens with fluoropyrimidine plus oxaliplatin alone, irinotecan, and/or monoclonal antibodies. Around 85% of patients completed planned induction treatment.[24-28] Furthermore, there was no compromise in radiotherapy adherence or increased perioperative complications. Therefore, compliance in the ICAR trial was consistent with previous publications.

Please cite this article as: Juliana Ominelli et al, Induction Chemotherapy and Chemoradiotherapy Combined to ASA vs. Placebo for High-Risk Rectal Cancer: Results of a Randomized Trial, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2022.05.002

Figure 3 Continued



Number at risk				
ASA	9	8	3	0
PLACEBO	10	8	6	1

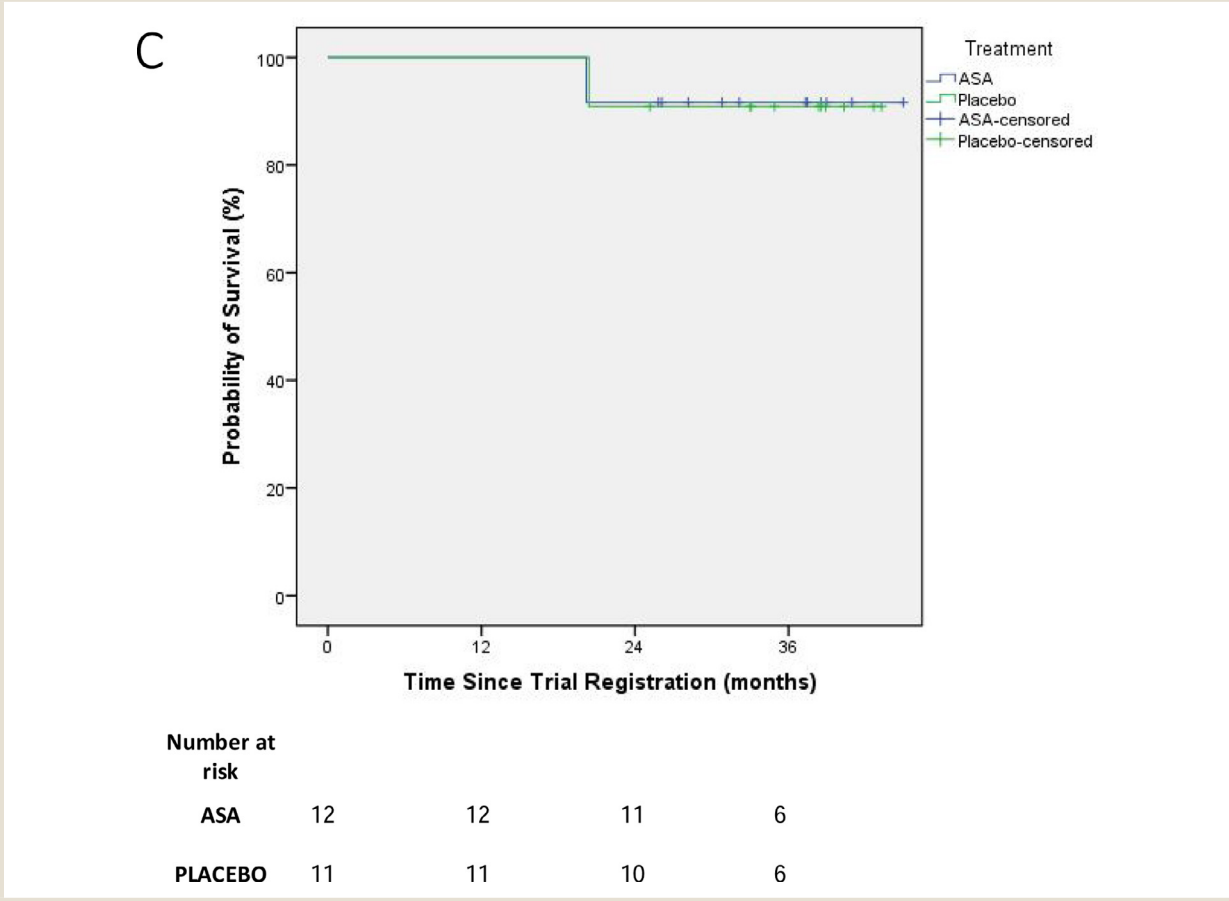
Patients who achieved pCR with neoadjuvant treatment have better PFS and OS.[29] In an attempt to improve these outcomes, intensified neoadjuvant treatment with IC and consolidation chemotherapy has been tested in high-risk locally advanced rectal cancer patients.[30] In patients who received IC with fluoropyrimidine plus oxaliplatin, 11% to 24% of patients achieved pCR.[25,26,31,32] Compared to standard CRT, only the PRODIGE 23 trial that evaluated FOLFIRINOX as IC showed higher pCR rates (27.5% vs. 11.7%, $P < .001$). [24] cCR is used as a surrogate for pCR. In 2004, Habr-Gama et al. proposed that patients with low rectal tumors and cCR could be spared from surgery.[33] The definition of cCR is based on the absence of tumors findings in clinical, endoscopic, and radiologic assessment. In the ICAR trial, the cCR rate of 30.4% was encouraging, especially considering patients with advanced tumors. In this trial, 66% had circumferential margin involvement, 37% were T4 tumors, 40% had EMVI, and 74% had nodal involvement at baseline. More than half of the patients had more than 4 high-risk factors. The proportion of patients (11%) who had distance progression during CRT was remarkable, consistent with the high-risk group profile. However, DFS and OS were similar to those found in other studies that evaluated total neoadjuvant treatment.

To our knowledge, this was the first randomized clinical trial to evaluate the role of ASA in the LACR neoadjuvant treatment. This treatment was safe and there was no increase in perioperative complications. Nevertheless, this trial has some limitations. First, few patients were evaluated in each arm. Since none of the arms reached the primary endpoint, the study was stopped at the first stage following the study design. Indeed, the choice of Simon's two-stage was chosen to minimize patient's exposure to a low active treatment. Second, ASA use was concise (less than 4 months). In Restivo et al. trial, patients used ASA for cardiovascular disease prevention with a median use of 5 years. [17] The studies that showed a reduction of colorectal adenomas and adenocarcinomas incidence [9,10] and lower incidence of tumor metastasis in CRC patients also had long-term use of ASA. [11] Perhaps the lack of benefit of using ASA was related to the short exposure to this drug.

In summary, the ICAR trial supports that IC followed by chemoradiotherapy is an optimal strategy for high-risk LARC. There was good compliance to treatment, a high rate of cCR, and a high sphincter-sparing approach. However, the addition of ASA showed no benefit with short-term use. Future research with ASA should focus on its long-term use.

Please cite this article as: Juliana Ominelli et al, Induction Chemotherapy and Chemoradiotherapy Combined to ASA vs. Placebo for High-Risk Rectal Cancer: Results of a Randomized Trial, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2022.05.002

Figure 3 Continued



Clinical Practice Points

- Induction chemotherapy allows better adherence than adjuvant chemotherapy without compromising tolerance to chemoradiotherapy (CRT). Moreover, it is expected to treat micro metastasis early, decrease toxicity, and improve downstaging.
- Acetylsalicylic acid (ASA) was associated with a lower incidence of metastasis in colorectal cancer patients. An observational study evaluated the role of chronic ASA use in stage II and III rectal cancer patients submitted to neoadjuvant CRT. It was found increased downstaging, higher pathological response, better progression-free survival (PFS), and overall survival (OS) in ASA group.
- ICAR trial was the first randomized clinical trial to evaluate the role of ASA in the LACR neoadjuvant treatment. This treatment was safe and there was no increase in perioperative complications. However, the addition of ASA showed no benefit with short-term use.
- Thereby, ASA should not be used to intensify neoadjuvant treatment.

Authors' Statements

All authors have read and approved the manuscript.

Acknowledgments

We acknowledge the contributions of all members of the Division of Clinical Research and IMEC (Pernambuco, Brazil) pharmaceutics for providing ASA/placebo pills.

Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Sauer R, Becker H, Hohenberger W, et al. Preoperative vs. postoperative chemoradiotherapy for rectal cancer. *New Eng J Med*. 2004;351:1731–1740. doi:10.1056/NEJMoa040694.
2. Allegra CJ, Yothers G, O'Connell MJ, et al. Neoadjuvant 5-FU or capecitabine plus radiation with or without oxaliplatin in rectal cancer patients: A phase III randomized clinical trial. *J Natl Cancer Inst*. 2015;107. doi:10.1093/jnci/djv248.
3. Carvalho C, Glynne-Jones R. Review Challenges behind proving efficacy of adjuvant chemotherapy after preoperative chemoradiation for rectal cancer. www.thelancet.com/oncology. 2017;18.
4. Diefenhardt M, Ludmir EB, Hofheinz RD, et al. Association of treatment adherence with oncologic outcomes for patients with rectal cancer a post hoc analysis of the CAO/ARO/AIO-04 Phase III randomized clinical trial supplemental content. *JAMA Oncol*. 2020;6:1416–1421. doi:10.1001/jamaoncol.2020.2394.
5. Hong YS, Nam BH, pyo KK, et al. Oxaliplatin, fluorouracil, and leucovorin vs. fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicenter, phase 2, randomized controlled trial. *Lancet Oncol*. 2014;15. doi:10.1016/S1470-2045(14)70377-8.

Please cite this article as: Juliana Ominelli et al, Induction Chemotherapy and Chemoradiotherapy Combined to ASA vs. Placebo for High-Risk Rectal Cancer: Results of a Randomized Trial, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2022.05.002

6. Hong YS, Kim SY, Lee JS, et al. Oxaliplatin-based adjuvant chemotherapy for rectal cancer after preoperative chemoradiotherapy (ADORE): long-term results of a randomized controlled trial. *J Clin Oncol*. 2019;37. doi:10.1200/JCO.19.00016.
7. Chau I, Brown G, Cunningham D, et al. Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging-defined poor-risk rectal cancer. *J Clin Oncol*. 2006;24:668–674. doi:10.1200/JCO.2005.04.4875.
8. Fernández-Martos C, Pericay C, Aparicio J, et al. Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, l. *J Clin Oncol*. 2010;28:859–865. doi:10.1200/JCO.2009.25.8541.
9. Kune GA, Kune S, Watson LF. Colorectal cancer risk, chronic illnesses, operations, and medications: case control results from the Melbourne Colorectal Cancer Study. *Cancer Res*. 1988;48:4399–4404.
10. Flossmann E, Rothwell PM. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomized and observational studies. *Lancet*. 2007;369:1603–1613. doi:10.1016/S0140-6736(07)60747-8.
11. PM R, M W, JF P, JF B, TW M, Z M. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. *Lancet*. 2012;379:1591–1601. doi:10.1016/S0140-6736(12)60209-8.
12. Fu J, Xu Y, Yang Y, Liu Y, Ma L, Zhang Y. Aspirin suppresses chemoresistance and enhances antitumor activity of 5-Fu in 5-Fu-resistant colorectal cancer by abolishing 5-Fu-induced NF-κB activation. *Scientific Rep*. 2019;9. doi:10.1038/s41598-019-53276-1.
13. Kawamori T. Enhancement of colon carcinogenesis by prostaglandin E2 administration. *Carcinogenesis*. 2003;24. doi:10.1093/carcin/bgg033.
14. Wang D, Wang H, Shi Q, et al. Prostaglandin E2 promotes colorectal adenoma growth via transactivation of the nuclear peroxisome proliferator-activated receptor δ. *Cancer Cell*. 2004;6. doi:10.1016/j.ccr.2004.08.011.
15. Honn Kv, DG Tang, Crissman JD. Platelets and cancer metastasis: A causal relationship? *Cancer Metastasis Rev*. 1992;11. doi:10.1007/BF01307186.
16. Gupta GP, Massagué J. Platelets and metastasis revisited: a novel fatty link. *J Clin Invest*. 2004;114. doi:10.1172/JCI23823.
17. Restivo A, Cocco IMF, Casula G, et al. Aspirin as a neoadjuvant agent during preoperative chemoradiation for rectal cancer. *Brit J Cancer*. 2015;113:1133. doi:10.1038/BJC.2015.336.
18. Hofheinz RD, Wenz F, Post S, et al. Chemoradiotherapy with capecitabine vs. fluorouracil for locally advanced rectal cancer: a randomized, multicentre, non-inferiority, phase 3 trial. *Lancet Oncol*. 2012;13:579–588. doi:10.1016/S1470-2045(12)70116-X.
19. Patel UB, Taylor F, Blomqvist L, et al. Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience. *J clin oncol*. 2011;29:3753–3760. doi:10.1200/JCO.2011.34.9068.
20. Habr-Gama A, Sabbaga J, Gama-Rodrigues J, et al. Watch and wait approach following extended neoadjuvant chemoradiation for distal rectal cancer: are we getting closer to anal cancer management? *Dis Colon Rectum*. 2013;56:1109–1117. doi:10.1097/DCR.0b013e3182a25c4e.
21. Patel UB, Taylor F, Blomqvist L, et al. Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience. *J Clin Oncol*. 2011;29:3753–3760. doi:10.1200/JCO.2011.34.9068.
22. Mandard A -M, Dalibard F, Mandard J -C, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer*. 1994;73:2680–2686. doi:10.1002/1097-0142(19940601)73:11⟨2680::AID-CNCR2820731105⟩3.0.CO;2-C.
23. Cohen R, Vernerey D, Bellera C, et al. Guidelines for time-to-event endpoint definitions in adjuvant randomized trials for patients with localized colon cancer: Results of the DATECAN initiative. *Euro J Cancer*. 2020;130:63–71. doi:10.1016/j.ejca.2020.02.009.
24. Conroy T, Bosset JF, Etienne PL, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22:702–715. doi:10.1016/S1470-2045(21)00079-6.
25. Chau I, Brown G, Cunningham D, et al. Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging–defined poor-risk rectal cancer. *J Clin Oncol*. 2006;24. doi:10.1200/JCO.2005.04.4875.
26. Dewdney A, Cunningham D, Tabernero J, et al. Multicenter randomized phase ii clinical trial comparing neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-C). *J Clin Oncol*. 2012;30. doi:10.1200/JCO.2011.39.6036.
27. Nogué M, Salud A, Vicente P, et al. Addition of bevacizumab to XELOX induction therapy plus concomitant capecitabine-based chemoradiotherapy in magnetic resonance imaging–defined poor-prognosis locally advanced rectal cancer: The AVACROSS study. *Oncologist*. 2011;16. doi:10.1634/theoncologist.2010-0285.
28. Masi G, Vivaldi C, Fornaro L, et al. Total neoadjuvant approach with FOLFOXIRI plus bevacizumab followed by chemoradiotherapy plus bevacizumab in locally advanced rectal cancer: the TRUST trial. *Euro J Cancer*. 2019;110. doi:10.1016/j.ejca.2019.01.006.
29. Wan T, Zhang XF, Liang C, Liao CW, Li JY, Zhou YM. The prognostic value of a pathologic complete response after neoadjuvant therapy for digestive cancer: systematic review and meta-analysis of 21 studies. *Ann Surg Oncol*. 2019;26. doi:10.1245/s10434-018-07147-0.
30. Ominelli J, Valadão M, Araujo RO de C, Cristina de Melo A, Araujo LH. The evolving field of neoadjuvant therapy in locally-advanced rectal cancer: evidence and prospects. *Clin Colorectal Cancer*. 2021;20. doi:10.1016/j.clcc.2021.06.005.
31. Fokas E, Allgäuer M, Polat B, et al. Randomized phase II trial of chemoradiotherapy plus induction or consolidation chemotherapy as total neoadjuvant therapy for locally advanced rectal cancer: CAO/ARO/AIO-12. *J Clin Oncol*. 2019;37. doi:10.1200/JCO.19.00308.
32. Fernández-Martos C, Pericay C, Aparicio J, et al. Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant Capecitabine Plus Oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging–defined, locally advanced rectal cancer: grupo cáncer de recto 3 study. *J Clin Oncol*. 2010;28. doi:10.1200/JCO.2009.25.8541.
33. Habr-Gama A, Perez RO, Nadalin W, et al. Operative vs. nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy. *Ann Surg*. 2004;240. doi:10.1097/01.sla.0000141194.27992.32.

Please cite this article as: Juliana Ominelli et al, Induction Chemotherapy and Chemoradiotherapy Combined to ASA vs. Placebo for High-Risk Rectal Cancer: Results of a Randomized Trial, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2022.05.002